(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 111 864**
B1

(12) # EUROPEAN PATENT SPECIFICATION

(45) Date of publication of patent specification: **07.03.90**

(21) Application number: **83112480.5**

(22) Date of filing: **12.12.83**

(51) Int. Cl.[5]: **C 07 D 401/04**, C 07 D 403/04, A 61 K 31/55 // C07D403/12, C07D401/12, C07D211/58, C07D207/14, C07D211/72, C07D211/42, C07D207/12

(54) **1,4-Benzodiazepine derivatives.**

(30) Priority: **21.12.82 JP 225273/82**

(43) Date of publication of application:
27.06.84 Bulletin 84/26

(45) Publication of the grant of the patent:
07.03.90 Bulletin 90/10

(84) Designated Contracting States:
BE CH DE FR IT LI NL SE

(56) References cited:
DE-A-1 929 810
FR-A-2 341 316

The file contains technical information submitted after the application was filed and not included in this specification

(73) Proprietor: **SHIONOGI SEIYAKU KABUSHIKI KAISHA**
12, Dosho-machi, 3-chome Higashi-ku, Osaka-shi
Osaka 541 (JP)

(72) Inventor: **Sugasawa, Tsutomu**
5-21-19, Mikage Yamate Higashinada-ku
Kobe-shi Hyogo (JP)
Inventor: **Adachi, Makoto**
2285-6, Ichihara Heguri-cho
Ikoma-gun Nara (JP)
Inventor: **Sasakura, Kazuyuki**
530-37, Manganji-cho
Yamatokoriyama-shi Nara (JP)
Inventor: **Matsushita, Akira**
2-3-22, Fukaeminamimachi Higashinada-ku
Kobe-shi Hyogo (JP)
Inventor: **Eigyo, Masami**
2-10-7, Shikanodai Nishi
Ikoma-shi Nara (JP)

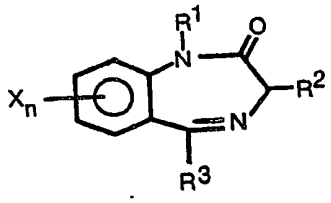
(74) Representative: **Hranitzky, Wilhelm Max et al**
NOVAPAT - CABINET CHEREAU 9, rue du Valais
CH-1202 Genève (CH)

Courier Press, Leamington Spa, England.

EP 0 111 864 B1

Description

The present invention relates to 1,4-benzodiazepine derivatives of the formula:



(I)

in which

R^1 is unsubstituted piperidinyl or optionally C_{1-3} alkyl-substituted pyrrolidinyl,

R^2 is hydrogen, hydroxy, or acetoxy,

R^3 is C_{1-3} alkyl, phenyl-C_{1-3} alkyl, or phenyl optionally substituted by one or two halogens,

X is hydrogen, halogen, C_{1-3} alkyl, C_{1-3}alkoxy, nitro, trifluoromethyl, or di-C_{1-3} alkyl-amino, and

n is 1 or 2

or pharmaceutically acceptable acid addition salts thereof, which are useful as antidepressants or anxiolytic agents.

1,4-benzodiazepine derivatives having a formula similar to that of the above-mentioned derivatives of the formula (I) are disclosed in DE—A—1 929 810. More particularly, DE—A—1 929 810 discloses 1-(1-ethyl-3-piperidinyl)-1,3-dihydro-2H-1,4-benzodiazepine-2-ones having anxiolytic, muscle relaxing and hypnotic activities. These known 1,4-benzodiazepine derivatives differ from the novel compounds of the present invention in that, in their formula, R^1 is piperidinyl substituted by an ethyl group, whereas, in the compounds of the present invention, R^1 is either unsubstituted piperidinyl or optionally C_{1-3} alkyl-substituted pyrrolidinyl.

It has been found that the novel 1,4-benzodiazepine derivatives of the above formula (I) are unexpectedly more potent in the antagonism of tetrabenazine-induced ptsosis in mice than the known compounds disclosed in DE—A—1 929 810.

Concrete examples of the terms used in the specification are illustratively shown below:

C_{1-3} alkyl refers to methyl, ethyl, propyl, and isopropyl,

C_{1-3} alkoxy refers to methoxy, ethoxy, propoxy, and isopropoxy,

di-C_{1-3} alkyl-amino refers to dimethylamino, diethylamino, dipropylamino, methylethylamino, methylpropylamino, and ethylpropylamino,

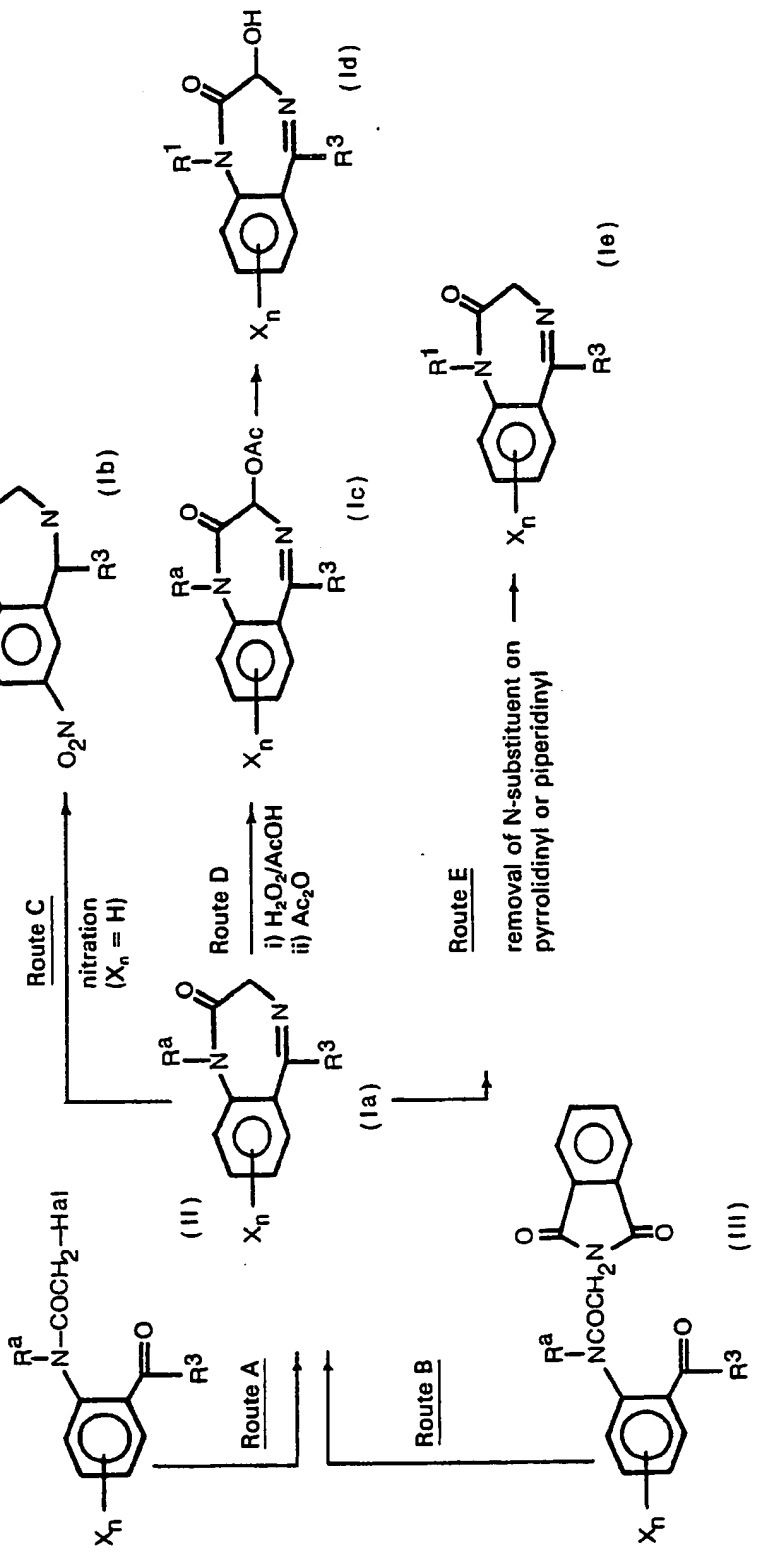
phenyl-C_{1-3} alkyl refers to benzyl, phenethyl, and phenylpropyl,

amino-protecting group refers to those ordinarily used in the peptide chemistry such as benzyloxycarbonyl, trityl, or t-butoxycarbonyl, and

halogen refers to fluorine, chlorine, bromine, or iodine.

The pharmaceutically acceptable acid addition salts of the objective compounds (I) illustratively include salts of an inorganic acid such as sulfuric acid, hydrochloric acid, hydrobromic acid, nitric acid or phosphoric acid and those of an organic acid such as acetic acid, citric acid, maleic acid, malic acid, succinic acid, tartaric acid, cinnamic acid, benzoic acid or methanesulfonic acid.

The objective compounds (I) can be prepared in accordance with the reaction scheme as shown below:

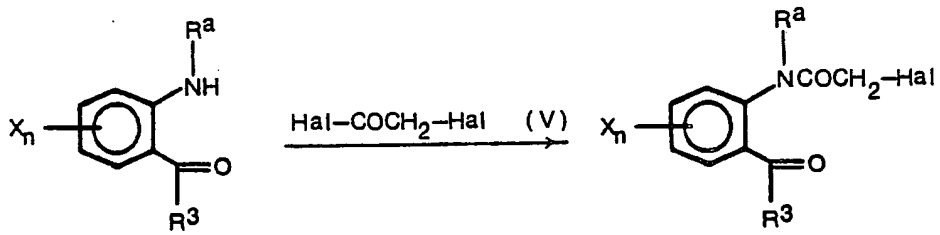

Route A
Route B
Route C
nitration
(Xn = H)
Route D
i) H2O2/AcOH
ii) Ac2O
Route E
removal of N-substituent on
pyrrolidinyl or piperidinyl
(II)
(III)
(Ia)
(Ib)
(Ic)
(Id)
(Ie)

in which Ac is acetyl, Hal is halogen, R^1 is unsubstituted piperidinyl or optionally C_{1-3} alkyl-substituted pyrrolidinyl, R^a is pyrrolidinyl or piperidinyl each optionally substituted by C_{1-3} alkyl, phenyl-C_{1-3} alkyl, C_{1-5} alkanoyl, C_{2-5} alkoxycarbonyl or protected by amino-protecting group, and R^3, X and n each is as defined above.

Route A

The compound (IA) which is a final desired product (i.e. a compound according to the invention, having the above indicated formula (I), in the case when R^a is unsubstituted pyrrolidinyl or piperidinyl or C_{1-3} alkyl-substituted pyrrolidinyl, or an intermediate compound, in the other cases, may be prepared by reacting the starting material (II) with an ammoniac reagent such as ammonia or ammonium carbonate. This reaction is performed in the range of temperature from about 15 to 150°C, preferably 40 to 90°C in an appropriate solvent such as acetonitrile, dimethylformamide, hexamethylphosphoric triamide, tetrahydrofuran, acetone, or methanol. For accelerating the reaction rate, the starting material (II) may be previously reacted with an alkali halide containing other more reactive halogen (e.g. potassium iodide, sodium iodide or lithium iodide) to lead to another more reactive halo-acetyl compound (IIa).

Further the starting material (II) may be prepared by reacting the corresponding anilino compound (IV) HCl with a haloacetyl halide (V) (e.g. chloroacetyl chloride or bromoacetyl bromide). If necessary, an organic base or inorganic base may be added as an appropriate acid-removing agent.



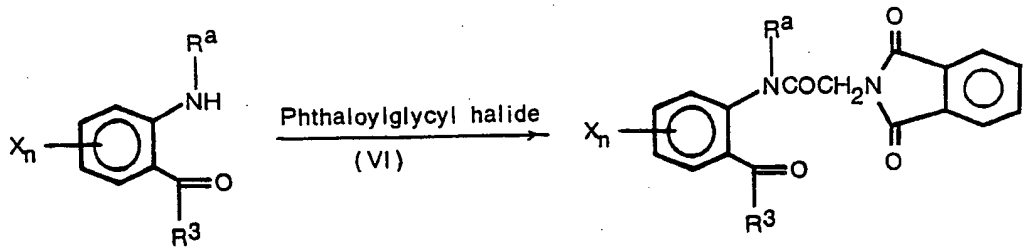
(IV) (II)

in which R^3, Hal, X, and n are as defined above, and R^a is pyrrolidinyl or piperidinyl each optionally substituted by C_{1-3} alkyl, phenyl-C_{1-3} alkyl, C_{1-5} alkanoyl, C_{2-5} alkoxycarbonyl, or protected by amino-protecting group.

Route B

The compound (Ia) may be prepared by reacting the starting material (III) with hydrazine or hydrazine hydrate. The present reaction is performed in the range of temperature from about 30 to 160°C, preferably 45 to 100°C in an appropriate solvent such as methanol, ethanol, chloroform, benzene, dimethylsulfoxide, or dimethylformamide according to the Gabriel synthesis. This reaction has an advantage that the reaction time is comparatively shorter but a disadvantage that the Smile rearrangement would eventually take place partially as a side reaction.

The starting material (III) may be, for example, prepared by reacting an anilino compound (IV) with a phthaloylglycyl halide (VI) in the presence of an organic or inorganic base such as triethylamine, pyridine, sodium hydride, potassium carbonate, sodium hydrogencarbonate, or potassium methoxide. The reaction is performed in an appropriate solvent in the range of temperature from room temperature to temperature under heating, for example, about 15 to 100°C.



(IV) (III)

in which R^1 is as given in Route A, and R^3, Hal, X and n are as given earlier.

Route C

Benzodiazepine (Ia) (X_n = H; R^a = unsubstituted pyrrolidinyl or piperidinyl or C_{1-3} alkyl-substituted pyrrolidinyl) is nitrated to afford the corresponding 7-nitro compound (Ib). The nitration is performed under cooling at about −30°C to 0°C using a customary nitrating agent such as conc. sulfuric acid-nitric acid mixture or conc. sulfuric acid-potassium nitrate mixture.

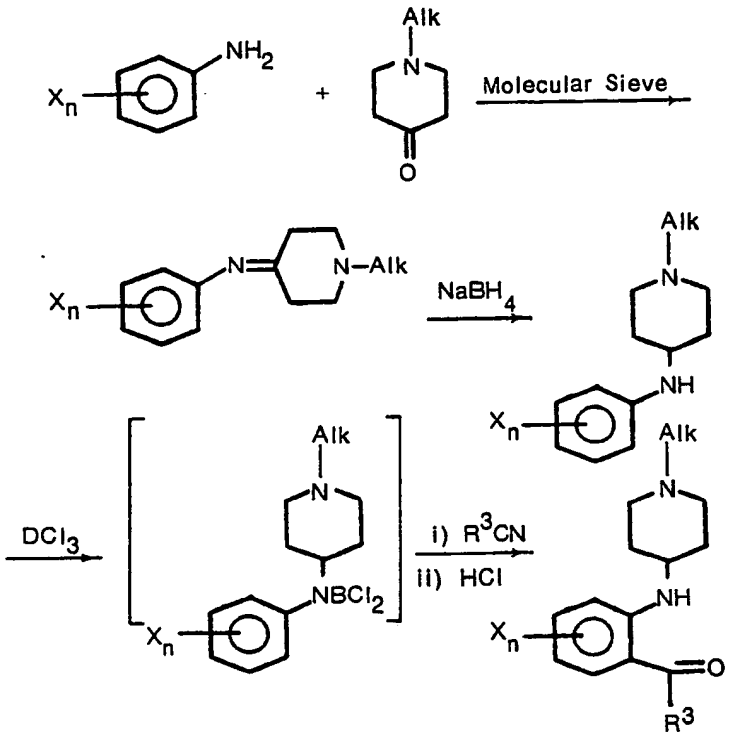
Route D

3-Hydroxybenzodiazepines (Id) can be prepared in a conventional manner, for example, by oxidizing the starting material (Ia) (R^a = N-protected pyrrolidinyl or piperidinyl) for N-oxidation, heating the resulting N-oxide with acetic anhydride for rearrangement to afford once the O-acetate (Ic) and hydrolyzing the acetoxy group in a solvent at temperature of about 15 to 120°C together with deprotection of the amino protecting group so as to obtain a final compound of formula (I) as above specified. It is sufficient therefor to perform the reaction at about room temperature (e.g. 15 to 25°C) in the aluminium chloride-anisole-nitromethane-methylene chloride system.

Route E

The 1-piperidinyl- or 1-pyrrolidinyl-benzodiazepines (Ie) can be prepared by subjecting the starting material (Ia) (R^a = pyrrolidinyl or piperidinyl each substituted by C_{1-3} alkyl, preferably methyl, or by C_{2-5} alkoxycarbonyl or protected by amino-protecting group) to removal of the N-substituent on the pyrrolidinyl or piperidinyl in a conventional manner such as in a solvent at temperature of about 15 to 150°C. For example, deprotection of benzyloxycarbonyl may be performed, using a strong acid such as hydrogen bromide-acetic acid mixture, trifluoroacetic acid or catalytic hydrogenation in addition to the aluminum chloride, anisole-nitromethane-methylene chloride system as described in Route D. Removal of trityl group can be attained by treating with dilute acetic acid. Dealkylation, in particular demethylation may be attained in a conventional manner by the methods already known, for example, by reacting an N-methyl compound with ethyl chlorocarbonate in the presence of diisopropylethylamine in a solvent such as benzene or toluene under refluxing and then heating the resulting N-ethoxycarbonyl compound under mild conditions with e.g. dialkyl sulfide and methanesulfonic acid.

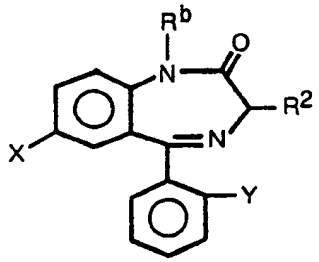
The starting material (IVa) can be prepared through the following synthetic route:



(IVa)

[Sugasawa et al., J. Am. Chem. Soc., *100*, 4842 (1978)].

A preferred compound of the formula (I) falling in the scope of the present invention is shown by the formula:



in which R^b is unsubstituted 4-piperidinyl or optionally C_{1-3} alkyl-substituted 3-pyrrolidinyl, R^2 is hydrogen or hydroxy, and X and Y each is hydrogen or halogen.

The objective compound (I) or its pharmaceutically acceptable acid addition salt is useful as a psychotropic agent such as antidepressant or anxiolytic agent. Results of the pharmacological experiments are below shown. Compound No. used in the following table corresponds to the number of Example, in which the same compound has been prepared.

Examples 1 to 22 show the preparation of the intermediate compound (Ia) whereas Examples 23 to 31 illustrate the preparation of the novel 1,4-benzodiazepine derivatives (I) which are the object of the present invention.

The following table shows that compounds Nos 23 and 26, i.e. 1,4-benzodiazepine derivatives of formula (I), in which R^1 is unsubstituted pyrrolidinyl or piperidinyl, are much more patent in the antagonism of tetrabenazine (TBZ) induced ptosis in mice than compounds Nos 6, 8, 10 and 15, i.e. 1,4-benzodiazepine derivatives of formula (Ia) in which R^a is 1-methyl-4-piperidinyl, and also than imipramine.

Compound No.	Acute Toxicity* (mg/kg, presumed)	Anti-TBZ ptosis** (ED_{50}, mg/kg)	Anti-PTZ*** convulsion (ED_{50}, mg/kg)
6	>200	0.26	>20
8	100—200	0.205	>10
10	>200	1.3	0.77
15	>200	0.839	>10
23	>200	0.075	8.52
26	>200	0.063	>10
imipramine	>200	0.799	>10

Note: Each compound was used in the form of 0.5 to 1% suspension made by mixing with its half volume of arabic gum.

*Acute toxicity test

To DS male mice in 4 to 5 weeks age was subcutaneously administered 100 to 200 mg of the test compound, and the number of dead mice was measured over a period of seven days. Result was shown by a presumed LD_{50} (mg/kg).

**Antagonism to the tetrabenazine (TBZ) induced ptosis

To several groups of DS male mice in 4 to 5 weeks age, each group consisting of 5 mice was subcutaneously administered the test compound. Half an hour later, 50 mg/kg of tetrabenazine was subcutaneously administered. Degree of the ptosis in 1 hour was scored, and the result was subjected to the rigid conversion. The ED_{50} value was obtained from the regression straight-line.

***Antagonism to the pentylenetetrazole (PTZ) induced convulsion

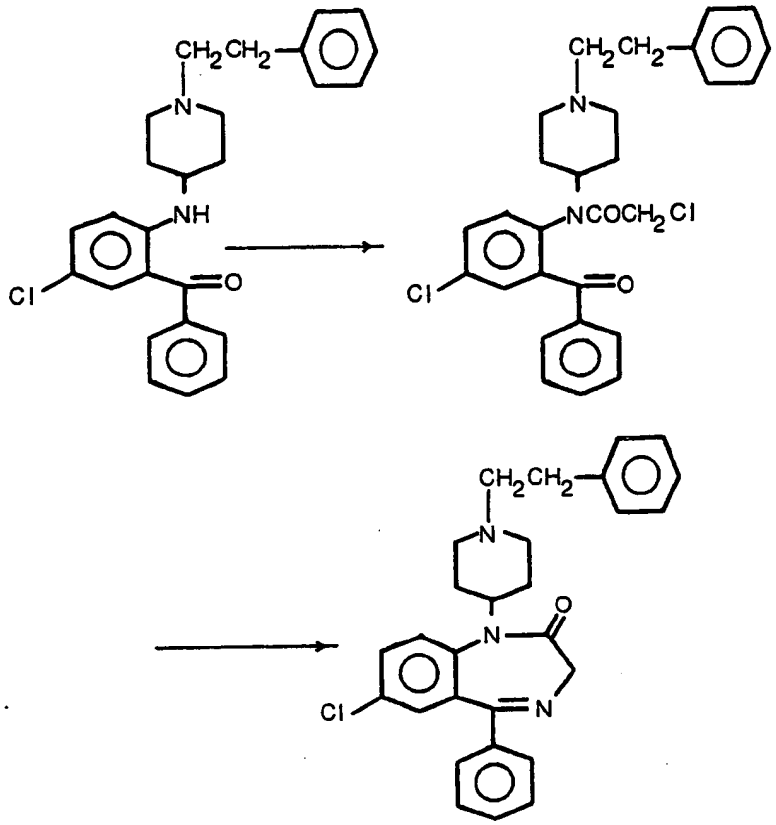
To several groups of ddy male mice in 4 to 5 weeks age, each group consisting of 8 mice was orally administered the test compound. Half an hour later, 125 mg/kg of pentylenetetrazole was subcutaneously administered, and the number of mice surviving during 2 hours was observed. The ED_{50} value was obtained from the survival number according to the probit method.

The objective compounds (I) or their pharmaceutically acceptable acid addition salts may be administered singly or together with appropriate carriers, diluents, and/or excipients such as wheat starch, corn starch, potato starch or gelatin. The choice of a carrier, diluent, and/or excipient will be decided, depending upon the preferred route of administration, solubility of the compound used as an effective ingredient, and pharmaceutical standard practice. Exemplary preparations are tablets, capsules, pills, suspensions, syrups, powders, solutions, suppositories, and these preparations may be formulated in a conventional manner. Daily oral dosage of the objective compound (I) or its pharmaceutically acceptable salt to adult humans when available as an antidepressant or anxiolytic agent is about 0.1 to 300 mg.

Presently preferred and practical embodiments of the present invention are illustratively shown in the following examples and referential examples.

Example 1

(Preparation of an intermediate compound Ia)

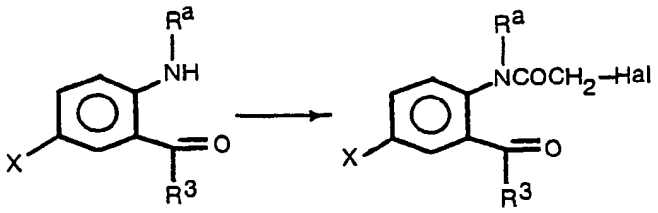


A mixture of 4-(4-chloro-2-benzoylanilino)-1-phenethylpiperidine hydrochloride (2.85 g, 5.9 mmol) and 2-chloroacetyl chloride (0.94 ml, 5.9 × 2 mmol) in acetonitrile (20 ml) is refluxed under heating over a period of 1 hour, and the reaction mixture is concentrated in vacuo. The residue is mixed with sodium iodide (2.6 g, 5.8 × 3 mmol) and acetonitrile (50 ml), and the resultant mixture is stirred at 70°C (bath temp.) over a period of 2.5 hours. After cooling, the reaction mixture is mixed with ammonium carbonate (6 g) and stirred at room temperature over a period of 10 days. The reaction mixture is concentrated in vacuo, and the residue is mixed with water and extracted with methylene chloride. The methylene chloride layer is washed with water, dried over anhydrous potassium carbonate and concentrated in vacuo. The residue is chromatographed on a column of alumina, which is eluted with benzene containing 5% ethyl acetate. The eluate is concentrated in vacuo to give an oil (2.28 g), which is again purified by the same chromatography as above to give 7-chloro-1,3-dihydro-1-(1-phenethyl-4-piperidinyl)-5-phenyl-2H-1,4-benzodiazepin-2-one (1.75 g) as an oil. The yield is 67%. The oxalate, mp. 217—219°C dec. (ethanol).

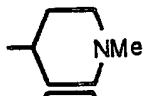
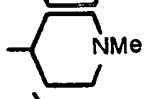
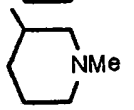
Intermediary chloroacetamide hydrochloride, mp. 235—238°C (dec.).

Examples 2—4

The reactions are performed as in Example 1, whereby the following intermediate (IIa) compounds are prepared.



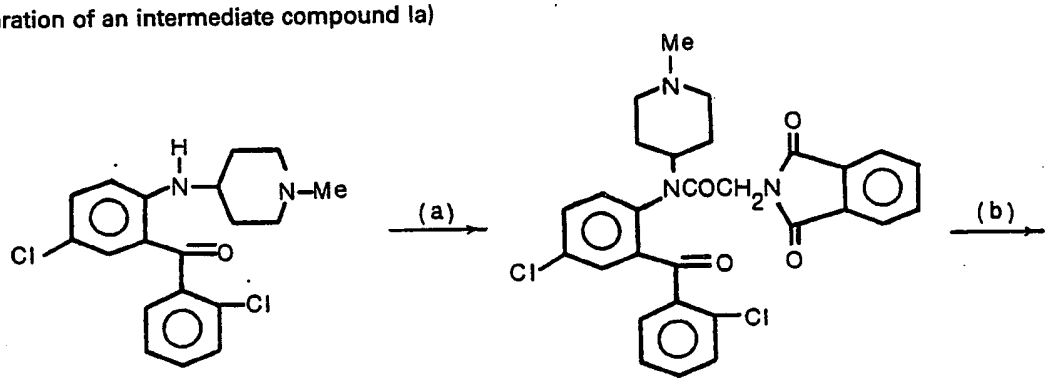
(IVa) (IIa)

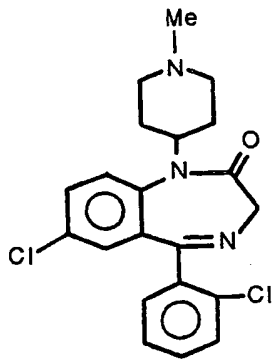
Ex. No.	IIa X	IIa R^a	IIa R^3	IIa Hal	IIa mp (°C)/ IR (cm^{-1})/ NMR (ppm)
2	H		Me	Cl	(Nujol) 1680
3	Cl		Ph	I	200—203d (HI)
4	Cl		2-Cl-Ph	Cl	($CDCl_3$) 2.2 (HCl)

Note: Me (methyl), Ph (phenyl), d (decomposition).
* The hydrochloride: mp. 242—247 dec.

Example 5

(Preparation of an intermediate compound Ia)





a) A mixture of 4-[2-(2-chlorobenzoyl)-4-chloroanilino]-1-methylpiperidine (1.5 g; 4.13 mmol) and phthaloylglycyl chloride (1.85 g, 4.13 × 2 mmol) in acetonitrile (20 ml) is refluxed over a period of 48 hours, and the reaction mixture is concentrated in vacuo. The residue is mixed with ice — 2N sodium hydroxide mixture and benzene, and the resultant mixture is stirred at room temperature over a period of half an hour. The benzene layer is separated, and the aqueous layer is extracted with benzene. The benzene layers are combined, washed with water, dried over anhydrous potassium carbonate, and concentrated in vacuo. The residue is chromatographed on a column of alumina, which is eluted with benzene and methylene chloride. The latter part of the benzene eluate and the methylene chloride eluate are combined and concentrated in vacuo and crystallized from methylene chloride-acetone to give N-[4-chloro-2-(2-chlorobenzoyl)phenyl]-N-[4-(1-methylpiperidinyl)]phthaloylglycinamide (926 mg) as crystals melting at 215 to 216°C. The yield is 65%.

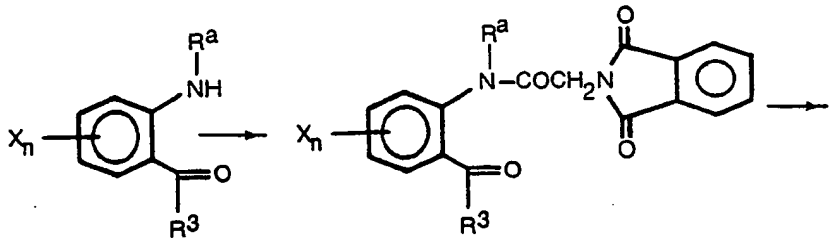
b) A mixture of said product (1.47 g, 2.67 mmol) and 80% hydrazine hydrate (0.39 ml, 2.67 × 3 mmol) in 95% ethanol is refluxed over a period of half an hour. After cooling, the reaction mixture is mixed with

benzene, and the precipitated crystals are filtered off. The filtrate is concentrated in vacuo, and the residue is chromatographed on a column of alumina, which is eluted with benzene and benzene-ethylacetate (1:1) mixture. The eluates are combined and concentrated in vacuo, and the residue is crystallized from ether to give 7-chloro-5-(2-chlorophenyl-1,3-dihydro-1-(1-methyl-4-piperidinyl)-2H-1,4-benzodiazepin-2-one (694 mg) as crystals melting at 146 to 147°C. The yield is 65%.

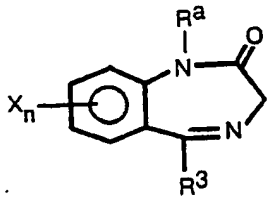
Examples 6—22

(Preparation of intermediate compounds Ia)

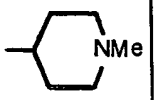
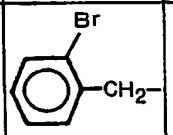
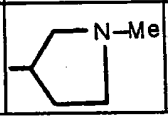
The reactions are performed as in Example 5, whereby the following intermediate compounds (III) and (Ia) are prepared.



(IV) (III)

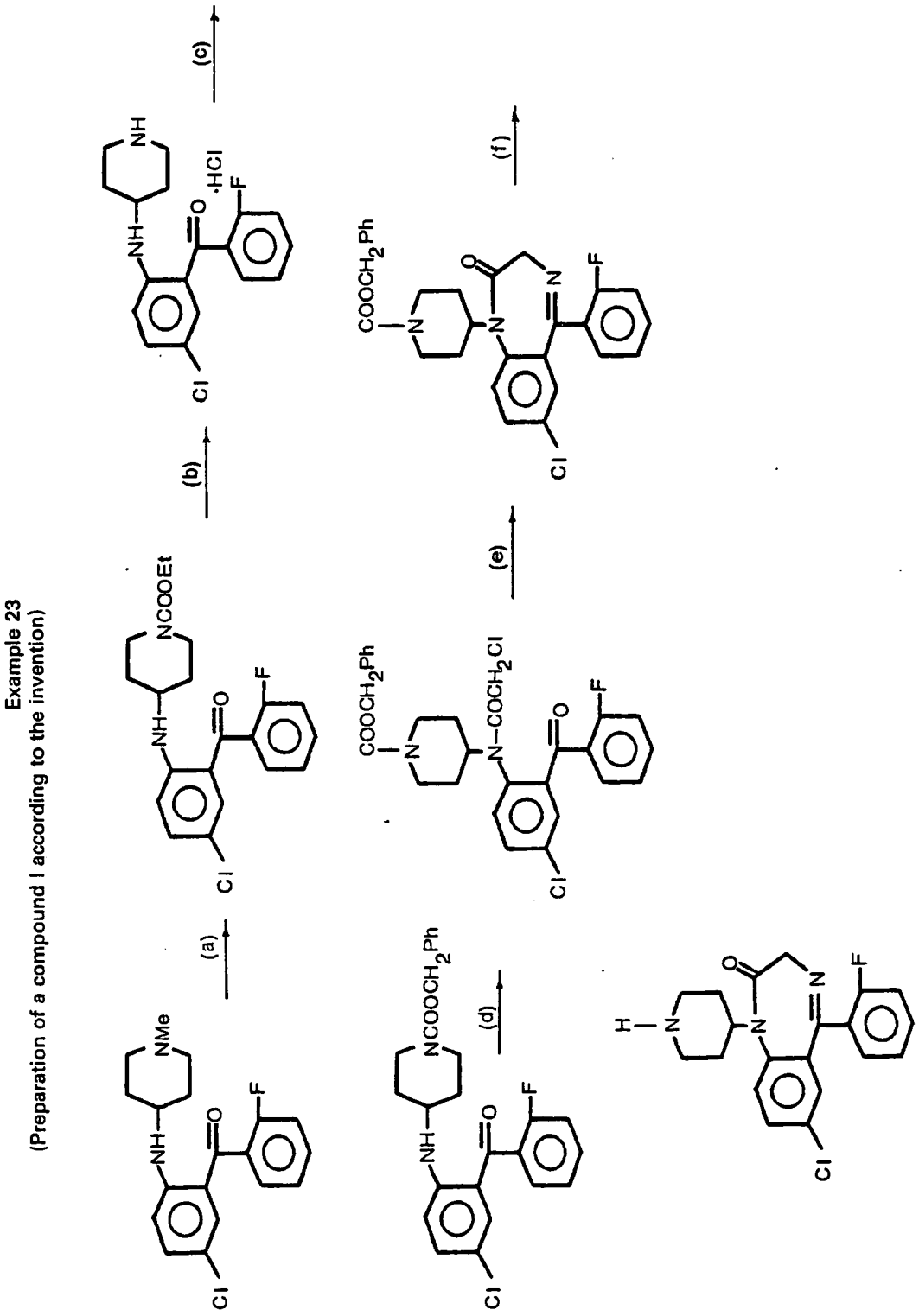


(Ia)

Ex. No.	III				Ia		
	X_n	R^a	R^3	mp (°C)/ IR (cm^{-1})	X_n	Yield	mp (°C)/ IR (cm^{-1})
6	H		Ph	1770 1720 (Nujol) 1660	H	59	157—159
7	4-MeO	"	2-F-Ph	1770 1720 ($CHCl_3$) 1630	7-MeO	68	76—77
8	H	"	"	194—195	H	48	123—125
9	"	"	4-F-Ph	1770 1720 (Nujol) 1660	"	80	1675 ($CHCl_3$)
10	4-Cl	"	2-F-Ph	1775 1720 ($CHCl_3$) 1675	7-Cl	72	147—149 198—200 ($HCl \cdot H_2O$)
11	5-CF_3	"	"	256—258	8-CF_3	41	121—122
12	5-Cl	"	"	253—254	8-Cl	22	203—203d
13	5-F	"	"	229—230	8-F	60	200—201
14	4-Br	"	"	141—143	7-Br	42	170—171
15	4-Me	"	"	1665 1710 (Nujol) 1655	7-Me	59	139—141
16	4-F	"	"	182—183	7-F	61	146—147
17	4,5-di-Cl	"	"	228—229	7,8-di-Cl	28	168—169
18	4-Me_2N	"	"	200—202	7-Me_2N	58	142—144
19	6-Cl	"	"	228—230	9-Cl	14	181—182
20	4-Cl	"	3-Cl-Ph	130—133d	7-Cl	71	172—173
21	H	"		amorphous* powder	H	62	230—234d (fumarate)
22	4-Cl		2-Cl-Ph	1780 1730 ($CHCl_3$) 1680	7-Cl	20	141—143

* NMR: $\delta_{ppm}^{CDCl_3}$: 22 (s, 3H), 3.97, 4.30 (q, J=16Hz, 2H), 4.43 (d, 2H).
Note: MeO (methoxy).

Example 23
(Preparation of a compound I according to the invention)



a) A mixture of 4-[4-chloro-2-(2-fluoro-benzoyl)anilino]-1-methylpiperidine (5.21 g, 15 mmol), ethyl chlorocarbonate (4.30 ml, 15 × 3 mmol) and diisopropylethylamine (2.61 ml, 15 mmol) in benzene (50 ml) is refluxed over a period of 1 hour. After cooling, the reaction mixture is mixed with icy waters, and the benzene layer is separated, washed with water, dried over anhydrous magnesium sulfate and concentrated in vacuo to give a crystalline residue (6.35 g). The substance is recrystallized from ether-petroleum ether to give 4-[4-chloro-2-(2-fluoro-benzoyl)anilino]-1-ethoxycarbonylpiperidine as crystals melting at 112 to 114°C.

b) A mixture of said product (6.35 g) obtained in Step (a) and conc.hydrochloric acid-water (1:1) mixture (50 ml) is refluxed over a period of 20 hours. The reaction mixture is concentrated in vacuo to give 4-[4-chloro-2-(2-fluorobenzoyl)anilino]piperidine hydrochloride (5.51 g) as crystals melting at 225 to 228°C.

c) To a suspension of above product (5.51 g) in a mixture of dioxane (50 ml) and 2N sodium hydroxide (19 ml) is dropwise added a solution of benzyl chlorocarbonate (4 ml, 12.7 × 2.2 mmol) in dioxane (10 ml) with ice-cooling and stirring, and the resultant mixture is stirred at room temperature over a period of half an hour. Water is added to the reaction mixture, and the mixture is shaken with benzene. The benzene layer is washed with water, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue (7.74 g) is purifed on Lobar® column B, which is eluted with ethyl acetate-methylene chloride (1:10 v/v). The eluate is concentrated in vacuo to afford 4-[4-chloro-2-(2-fluorobenzoyl)anilino]-1-benzyloxycarbonyl-piperidine (5.93 g) as an oil.

IR, $\nu_{max}^{CHCl_3}$, 3330 (NH), 1690, 1625 (CO) cm^{-1}.

d) A mixture of above product (5.93 g, 12.7 mmol) obtained in Step (c) and 2-chloroacetyl chloride (2.0 ml, 12.7 × 2 mmol) in benzene (50 ml) is refluxed over a period of 20 hours. The reaction mixture is concentrated in vacuo to give 4-[N-chloroacetyl-4-chloro-2-(2-fluorobenzoyl)anilino]-1-benzyloxycarbonyl-piperidine (6.9 g) as colorless powders.

^{1}H NMR, $\delta_{ppm}^{CDCl_3}$: 3.73, 4.00 (ABq, J=12Hz, COCH_2Cl), 5.0 (2H, s, OCH_2Ph).

e) A mixture of this product (6.9 g, 12.5 mmol) and sodium iodide (2.2 g, 12.5 × 1.2 mmol) in acetonitrile (50 ml) is heated at 70°C over a period of an hour. The reaction mixture is concentrated in vacuo, and the residue is extracted with benzene. The benzene layer is washed with water, dried over anhydrous magnesium sulfate, and concentrated in vacuo to give 4-[N-iodoacetyl-4-chloro-2-(2-fluoro-benzoyl)anilino]-1-benzyloxycarbonyl-piperidine (8.1 g) as an oil.

^{1}H NMR, $\delta_{ppm}^{CDCl_3}$: 3.33, 3.80 (ABq, J=10Hz, COCH_2I).

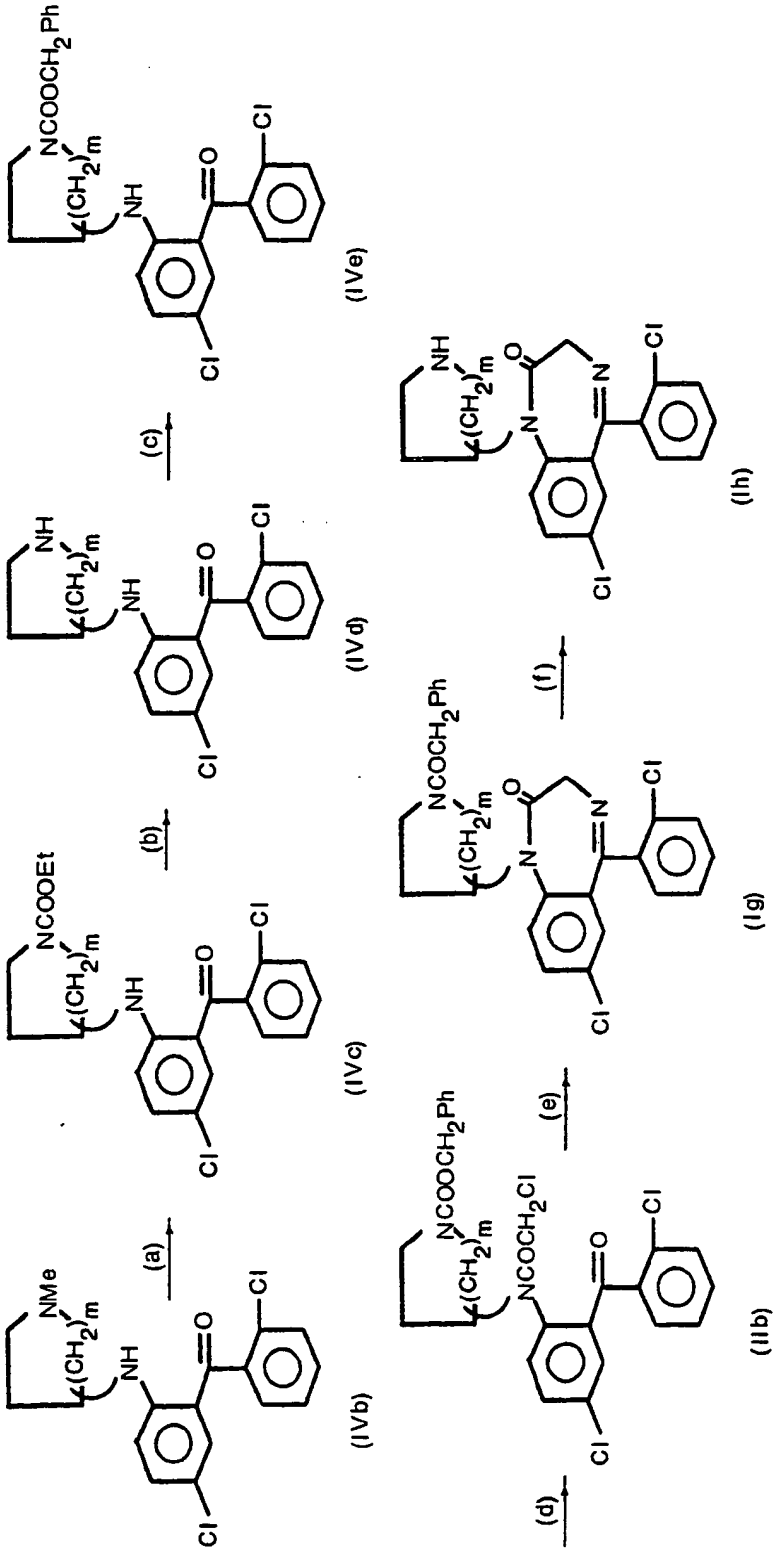
A mixture of above product (8.1 g), ammonium carbonate (14 g) and acetonitrile (20 ml) is heated in a sealed tube at 50°C (bath temp.) over a period of 60 hours. After cooling, the reaction mixture is mixed with water and shaken with methylene chloride. The methylene chloride layer is washed with water, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue is purified on Lobar® column B, which is eluted with 10—20% ethyl acetate-methylene chloride mixture. Evaporation of the eluate affords 1-(1-benzyloxycarbonyl-4-piperidinyl)-7-chloro-1,3-dihydro-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one (2.89 g) as colorless powders. The total yield is 45%.

f) A mixture of above product (2.89 g, 5.71 mmol), anisole (3.72 ml, 5.71 × 6 mmol), aluminum chloride (4.57 g, 5.7 × 6 mmol), methylene chloride (50 ml) and nitromethane (50 ml) is stirred at room temperature over a period of 20 hours. The reaction mixture is mixed with icy water and shaken with ether. The ether layer is shaken with dilute hydrochloric acid, and the aqueous layer is neutralized with 2N sodium hydroxide and extracted with ether. The ether layer is washed with ether, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue (2.04 g) is recrystallized from methanol-ethyl acetate to give 7-chloro-1,3-dihydro-5-(2-fluorophenyl)-1-(4-piperidinyl)-2H-1,4-benzodiazepin-2-one (1.61 g) as crystals melting at 197—199°C (dec.). The hydrobromide, mp. 261—262°C (dec.).

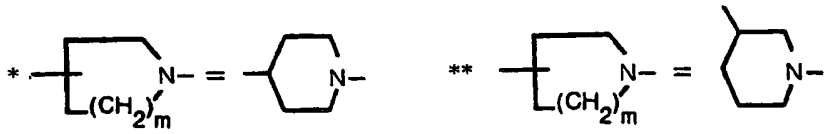
Example 24—25

(Preparation of compounds I)

The reactions are performed as in Example 23, whereby the following products are obtained.



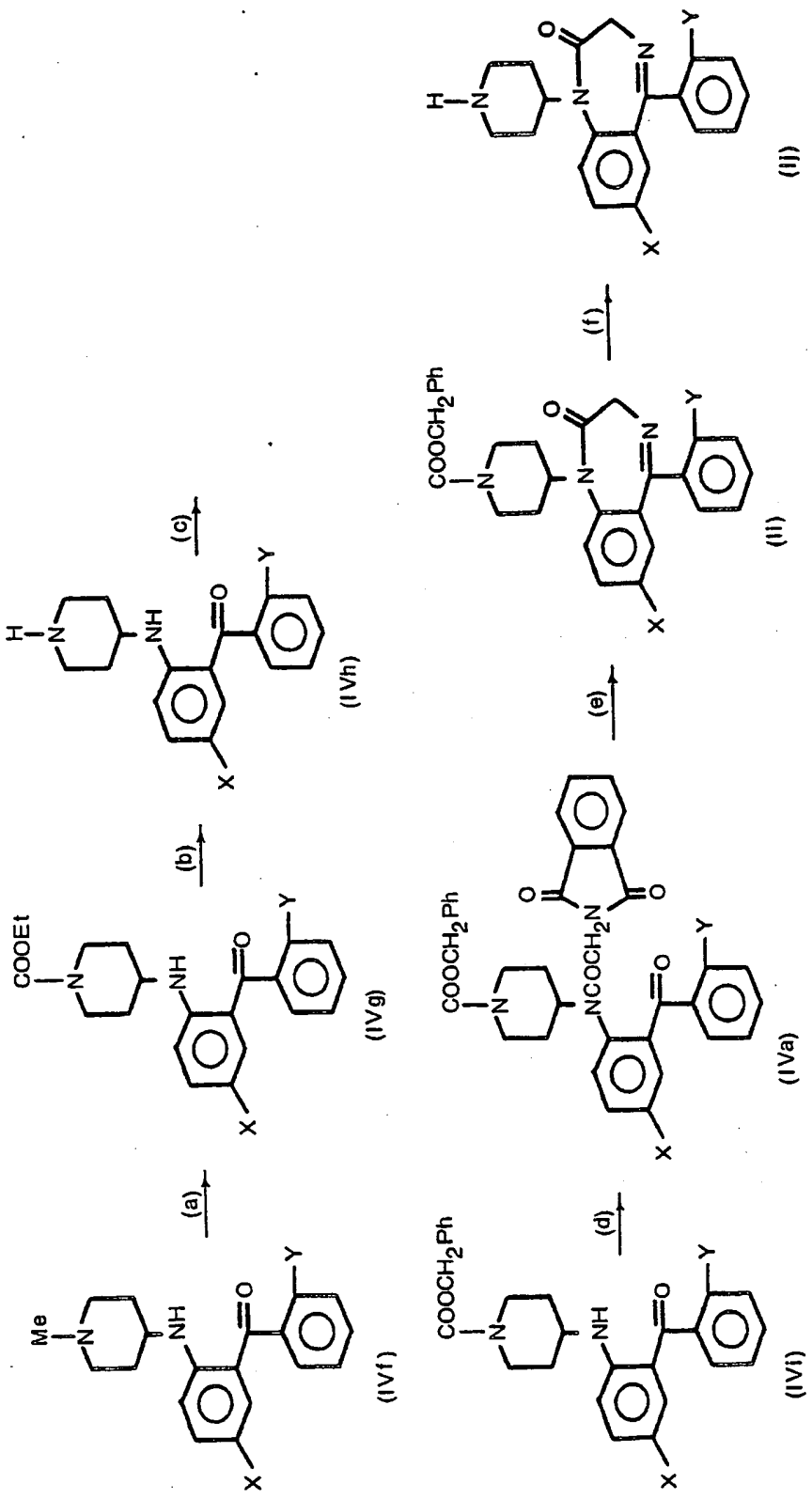
Example No.	24*		25**	
Compound Symbol	mp (°C)/IR (cm^{-1})	Yield (%)	mp (°C)/IR (cm^{-1})	Yield (%)
IVc	3227 1700 (film) 1630	quantitative	3333 ($CHCl_3$) 1670	quantitative
IVd	3300 (film) 1630	quantitative	3228 (film) 1620	quantitative
IVe	3227 1690 (film) 1620	quantitative	3227 1690 (film) 1620	75 (from IVb)
IIb	1680 (film)	quantitative	1690 (film)	quantitative
Ig	1670 ($CHCl_3$)	46 (from IVc)	1680 (film)	53 (from IVe)
Ih	95—100 3686 ($CHCl_3$) 1678	97 (from Ig)	133—136	34 (from IVb)



Examples 26—28

(Preparation of compounds I)

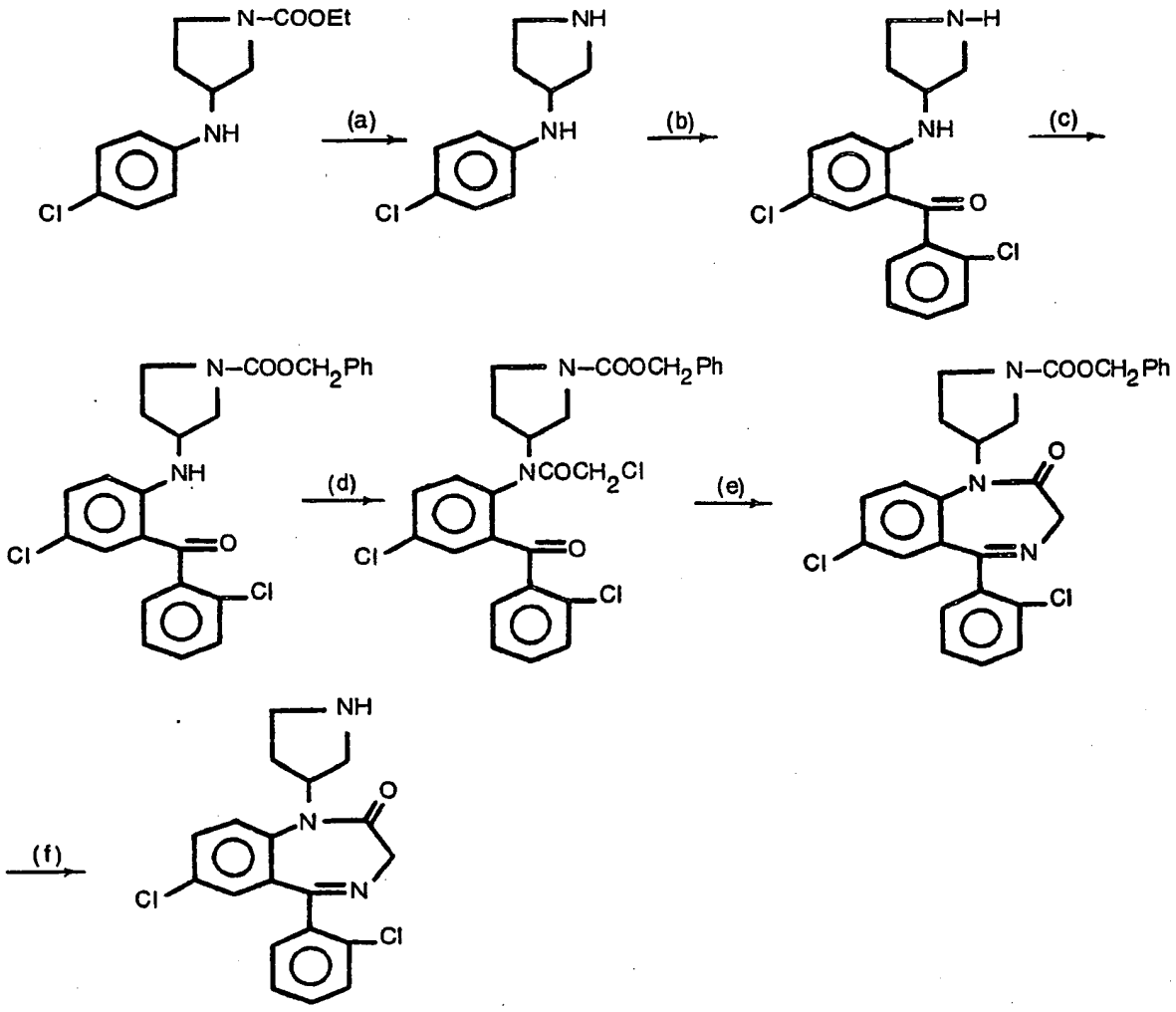
The reactions are performed according to Example 23 and partly to Example 5 (the part of the Gabriel Synthesis), whereby the following products are obtained.


(III)
(f)
(II)
(e)
(IVa)
(d)
(IVi)
(c)
(IVh)
(b)
(IVg)
(a)
(IVf)

Example No.	26*		27**		28***	
Compound Symbol	mp (°C)/IR (cm^{-1})	Yield (%)	mp (°C)/IR (cm^{-1})	Yield (%)	mp (°C)/IR (cm^{-1})	Yield (%)
IVg	3227 1700 (film) 1620	quantitative	3227 1690 (film) 1620	quantitative	3300 1700 (film) 1620	quantitative
IVh	3300 (film) 1630	quantitative	3300 (film) 1620	quantitative	240—241d (HCl)	97 (from IVf)
IVi	3227 1698 (film) 1615	94 (from IVg)	3227 1690 (film) 1620	98 (from IVg)	3228 1690 (film) 1620	quantitative
IIIa	1780 1720 (film) 1670	quantitative	1770 1720 (film) 1660	94 (from IVi)	148—149	82 (from IVi)
Ii	1680 (film)	80 (from IVi)	1680 (film)	89 (from IIIa)	130—131	89 (from IIIa)
Ij	281—283d (HBr)	60 (from IVf)	191—192****	75 (from IVf)	166—167	71 (from IVf)

* X = H, Y = H ** X = Cl, Y = H *** X = H, Y = F **** HBr H_2O, mp 262—265 (dec.).

Example 29



a) A mixture of ethyl 3-(4-chloroanilino)pyrrolidine-1-carboxylate (7.20 g) and conc. hydrochloric acid (72 ml) is heated under reflux over a period of 20 hours. The reaction mixture is concentrated in vacuo, and the residue is crystallized from methanol-isopropanol to give 3-(4-chloroanilino)pyrrolidine dihydrochloride (6.99 g) as crystals melting at 120 to 143°C. The yield is 96%.

b) To a suspension of above product (2.70 g, 10 mmol) and 2-chlorobenzonitrile (2.75 g, 20 mmol) in toluene (20 ml) is added a 1.23 M solution of boron trichloride (20 ml), and the resultant mixture is heated under reflux over a period of 1 hour. The reaction mixture is concentrated in vacuo to remove the solvent, and the residue is heated at temperature of 150°C over a period of 20 hours. After cooling, the residue is mixed with 2N hydrochloric acid (20 ml) and water (20 ml) and stirred under heating at 100°C (bath temp.). The reaction mixture is shaken with methylene chloride, and the organic layer is washed with 2N hydrochloric acid and dilute ammoniac solution in order, dried over anhydrous magnesium sulfate, and concentrated in vacuo to give crude 3-[4-chloro-2-(2-chlorobenzoyl)anilino]pyrrolidine as an oil.

c) As in the method of Example 19(c), above product is treated with benzyl chlorocarbonate (1.4 ml), 1N aqueous sodium hydroxide (10 ml) and tetrahydrofuran (30 ml), and the resulting crude product is purified from Lobar® column B, which is eluted with benzene-ethyl acetate (9:1 v/v) mixture. Evaporation of the eluate affords 3-[4-chloro-2-(2-chlorobenzoyl)anilino]-1-benzyloxycarbonylpyrrolidine (1.78 g) as an oil. The yield is 38%.

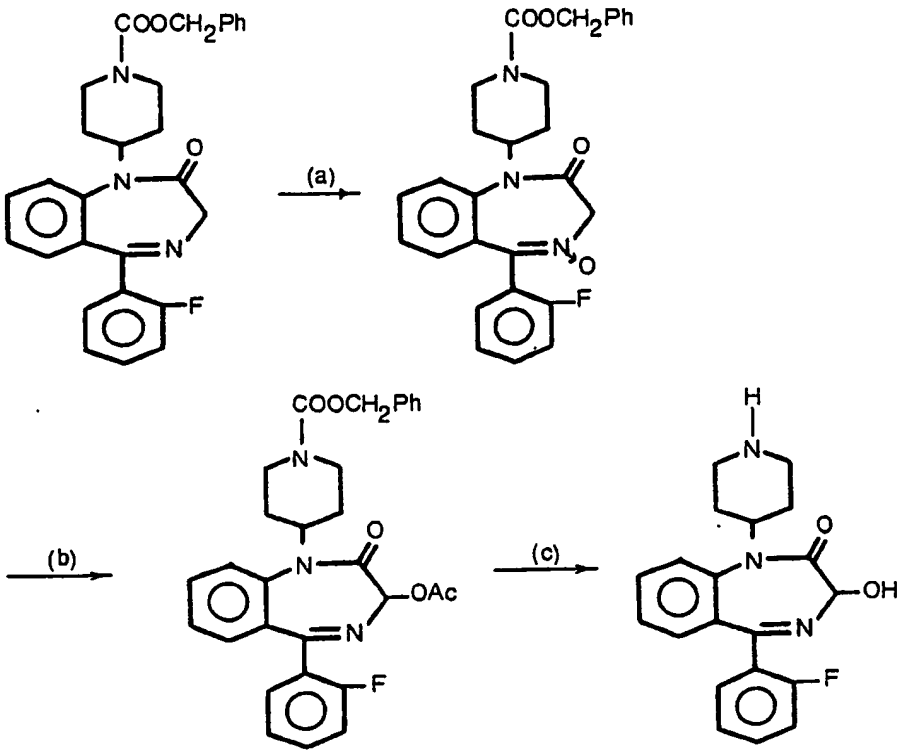
IR, $\nu_{max}^{CHCl_3}$, 3400 (NH), 1690, 1625 (CO) cm^{-1}.

^1H NMR, $\delta_{ppm}^{CDCl_3}$, 1.7—4.2 (m, aliphatic H), 5.12 (2H, s, OCH_2Ph), 6.6—7.5 (m, aromatic H), 9.1 (1H, d, J=6Hz, NH).

d) to f) The reactions are performed as in the method of Example 23, whereby the following products are obtained.

Step	Product	
	mp (°C)/IR (cm^{-1})	Yield (%)
d	1690 ($CHCl_3$)	96
e	1690 ($CHCl_3$)	43
f	138—140 (oxalate)	73

Example 30



a) To a solution of 1-(1-benzyloxycarbonyl-4-piperidinyl)-1,3-dihydro-5-(2-fluorophenyl)-2H-1,4-benzdiazepin-2-one (4.20 g, 8.91 mmol) in acetic acid (50 ml) is added 30% hydrogen peroxide (3.5 ml, 8.91 × 4.5 mmol), and the resultant mixture is heated at 65°C over a period of 16 hours. After cooling, the reaction mixture is mixed with sodium hydrogensulfite (3.5 g) and concentrated in vacuo to about its quartered volume. The concentrated solution is neutralized with ice-aqueous ammoniac solution and extracted with methylene chloride. The organic layer is washed with water, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue is chromatographed on a column of silica gel, which is eluted with ethyl acetate-benzene (1:1, v/v). The eluate is concentrated in vacuo to give the objective N-oxide (4.31 g) as an oil. The yield is 99%.

IR, $\nu_{max}^{CHCl_3}$: 1680 cm^{-1}.

^1H NMR, $\delta_{ppm}^{CDCl_3}$: 4.6 (2H, s, $COCH_2N\rightarrow O$), 5.1 (2H, s, OCH_2Ph).

b) A mixture of above N-oxide (4.31 g) and acetic anhydride (25 ml) is heated at 140°C (bath temp.) over a period of 1 hour, and the reaction mixture is concentrated in vacuo to remove the acetic anhydride. The residue is chromatographed on a column of silica gel, which is eluted with methylene chloride-ethyl acetate (5:1, v/v). The eluate is concentrated in vacuo to give 3-acetoxy compound (4.04 g) as an oil. The yield is 86%.

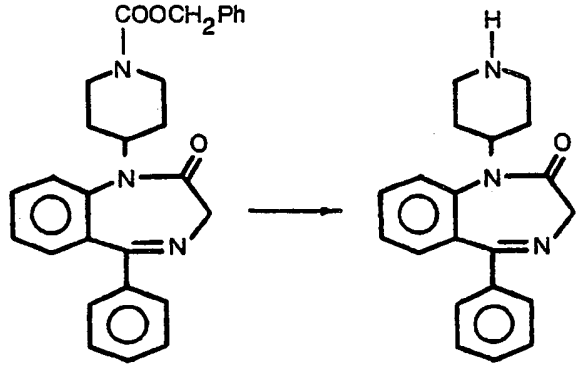
IR, $\nu_{max}^{CHCl_3}$: 1636, 1692 cm^{-1}.

^1H NMR, $\delta_{ppm}^{CDCl_3}$: 2.26 (3H, s, $OCOCH_3$), 5.10 (2H, s, OCH_2Ph),

5.90 (1H, s, $NCH(OAc)CO$).

c) Above 3-acetoxy compound (4.04 g) is reacted in the system of aluminum chloride, anisole, nitromethane and methylene chloride as in the method of Example 23(f). The product after extraction is crystallized from methylene chloride-ethyl acetate to give 1-(4-piperidinyl)-3-hydroxy-1,3-dihydro-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one (2.14 g) as crystals melting at 190 to 192°C. The yield is 79%.

Example 31



A mixture of 1-(1-benzyloxycarbonyl-4-piperidinyl)-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-1-one (17.6 g) obtained in Example 26(e) and trifluoroacetic acid (53 ml) is heated under reflux over a period of 2 hours, and the reaction mixture is concentrated in vacuo. The residue is mixed with ether (100 ml) and water (150 ml), and ether layer is separated. The aqueous layer is made alkaline with ammonia and extracted with methylene chloride. The methylene chloride layer is washed with water, dried over anhydrous magnesium sulfate, decolorized with active carbon, and concentrated in vacuo. The residue is dissolved in 90% ethanol (60 ml) and mixed with conc. hydrobromic acid (4.4 ml). The precipitated crystals are recrystallized from methanol to give 1-(4-piperidinyl)-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-1-one hydrobromide (12.4 g) as crystals melting at 282 to 283°C (dec.).

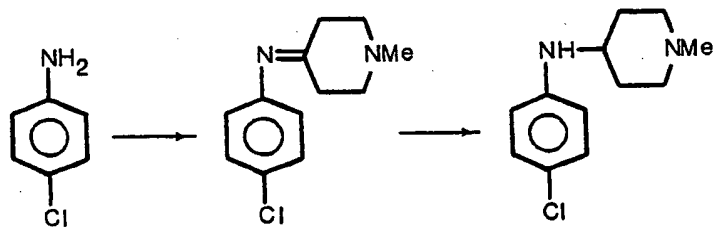
Formulation

Compound in Example 23	30 g
Wheat starch	240 g
Lactose	240 g

These are admixed evenly. A desired amount of 5% gelatin solution is added to the mixture, which is dried and sieved. The resultant granules are admixed with talc (30 g) and subjected to a tableting machine to give 3000 tablets, each weighing 180 mg and containing 10 mg of the effective ingredient.

Now, some further examples of the preparation of starting or intermediate products, useful in the preparation of the intermediate compounds (Ia), will be given as "Referential examples".

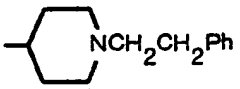
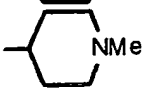
Referential Example 1



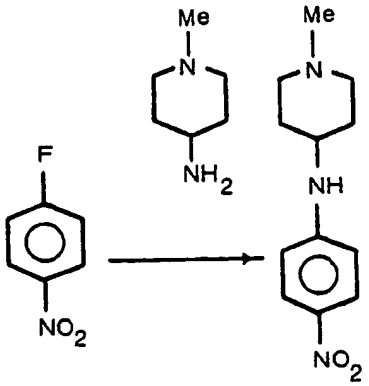
To a solution of 4-chloroaniline (4.59 g, 30 × 1.2 mmol) and 1-methyl-4-piperidone (3.39 g, 30 mmol) in benzene (12 ml) is added Molecular Sieve 4A (6 g), and the resultant mixture is heated under reflux over a period of 20 hours. After cooling, the reaction mixture is mixed with ether and filtered to remove the Molecular Sieve. The filtrate is concentrated in vacuo, and the residue is dissolved in 95% ethanol (50 ml). Sodium borohydride (0.6 g, 15 mmol) is added to the solution, which is stirred at room temperature over a period of 5 hours. The reaction mixture is mixed with water and the ethanol is evaporated therefrom. The aqueous residue is shaken with methylene chloride, and the methylene chloride layer is dried over anhydrous potassium carbonate and concentrated in vacuo. The residue is distilled to give crude product (5.89 g) b.p. 130—150°C/1 mm Hg. This substance is recrystallized from ether-petroleum ether to give 4-(4-chloroanilino)-1-methylpiperidine (5.25 g) as crystals melting at 91 to 92°C. The yield is 78%.

Referential Examples 2—13

The reactions are performed as in the method of Example 1, whereby the following products are obtained.

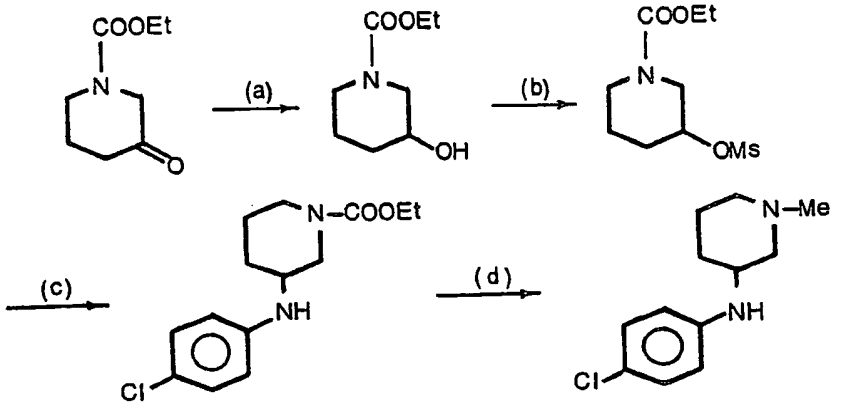
Ref. Ex. No.	X_n	R^a	Yield (%)	mp (°C)/ bp (°C/mm Hg)
2	4-Cl		74	83—84
3	H		78	82—83
4	3-Cl	"	73	110—121
5	4-MeO	"	82	180—145
6	4-$(Me)_2N$	"	60	139—141
7	3-F	"	71	104—106
8	3-CF_3	"	75	143—146/7
9	4-Br	"	19	85—87
10	4-Me	"	67	125—127
11	4-F	"	79	92—93
12	3,4-Cl,Cl	"	63	80—81
13	4-NO_2	"	56	153—155

Referential Example 14



A mixture of 4-amino-1-methylpiperidine (4.82 g, 32.3 mmol) and 4-fluoronitrobenzene (4.56 g, 32.3 mmol) is heated at 100°C on an oil bath over a period of 7 hours. After cooling, the reaction mixture is mixed with 2N hydrochloric acid (20 ml) and water (20 ml) and shaken with ether. The acidic layer is neutralized with conc. ammoniac solution and shaken with methylene chloride. The methylene chloride layer is washed with water, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue is crystallized from ether-petroleum ether to give 4-(4-nitroanilino)-1-methylpiperidine (4.27 g) as crystals melting at 153 to 155°C. The yield is 56%.

Referential Example 15



a) To a solution of ethyl 3-oxo-1-piperidine-1-carboxylate (6 g, 35 mmol) in methanol (60 ml) is added sodium borohydrate (1.34 g, 35 mmol), and the resultant mixture is stirred at room temperature over a period of 1 hour. The reaction mixture is mixed with icy water and shaken with methylene chloride. The organic layer is dried over anhydrous potassium carbonate and concentrated in vacuo to give ethyl 3-hydroxypiperidine-1-carboxylate (6.03 g) as an oil.

b) To a solution of above product in pyridine (40 ml) is added mesyl chloride (3.2 ml, 35 × 1.2 mmol) under ice cooling, and the resultant mixture is allowed to stand at room temperature over a period of 20 hours. The reaction mixture is mixed with icy water and shaken with ether. The organic layer is washed with water, dried over anhydrous sodium sulfate, and concentrated in vacuo to give ethyl 3-mesyloxy-piperidine-1-carboxylate (8.7 g) as an oil.

IR, ν_{max}^{film}: 1690 (N-COOEt), 1350, 1180(OSO_2) cm^{-1}.

^1H NMR, $\delta_{ppm}^{CDCl_3}$: 3.05 (3H, s, OSO_2CH_3).

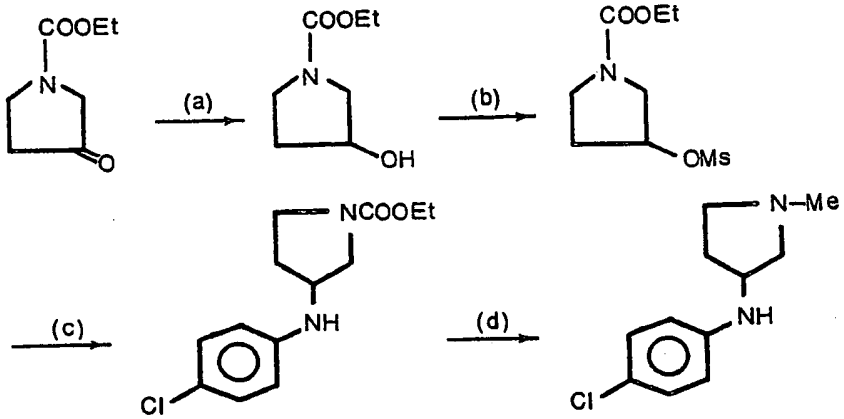
c) A mixture of above product (8.7 g, 35 mmol) and 4-chloroaniline (13.3 g, 35 × 3 mmol) is heated at 160°C over a period of half an hour. After cooling, the reaction mixture is mixed with icy water and extracted with ether. The ether layer is washed with water, dried over anhydrous sodium sulfate, and concentrated in vacuo. The remaining 4-chloroaniline is distilled off under reduced pressure. The residue is purified on Lobar® column B, which is eluted with chloroform:ethyl acetate (10:1 v/v). The eluate is concentrated to give ethyl 3-(4-chloroanilinopiperidine)-1-carboxylate (4.87 g) as an oil.

d) To a suspension of lithium aluminum hydride (1.96 g, 17.2 × 3 mmol) in ether (50 ml) is dropwise added a solution of above product (4.87 g) in ether (20 ml) under ice cooling, and the resultant mixture is refluxed over a period of half an hour under stirring. After cooling, the reaction mixture is mixed with hyhdrous ether and 6N aqueous sodium hydroxide (4 ml) successively, and the insoluble material is filtered off. The ether layer is concentrated in vacuo to give 3-(4-chloroanilino)-1-methylpiperidine (3.91 g) as an oil. The yield is 100%..

IR, ν_{max}^{film}: 3270 (NH) cm^{-1}.

^1H NMR, $\delta_{ppm}^{CDCl_3}$: 1.2—4.0 (m, aliphatic H), 2.3 (s, NCH_3), 6.4—7.3 (m, aromatic H).

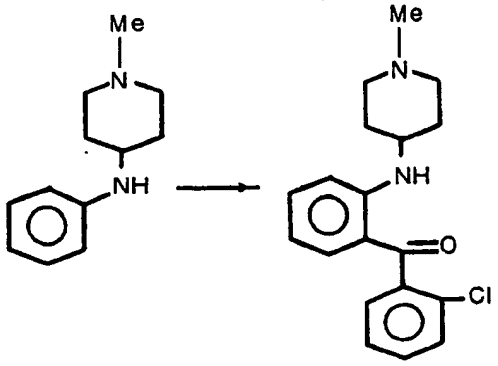
Referential Example 16



As in the method of Referential Example 15, the reactions are performed using ethyl 3-pyrrolidone-1-carboxylate, whereby the following products are prepared.

Step	Yield(%)	mp (°C)/IR (cm^{-1})
a	94	3420, 1680 (film)
b	84	1690, 1350, 1173 (film)
c	83	50—51
d	87	91—94

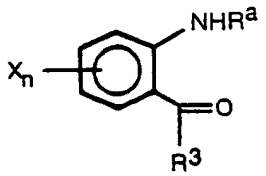
Referential Example 17



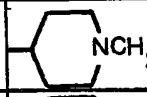
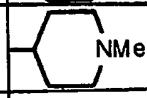
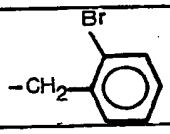
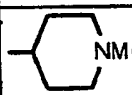
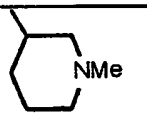
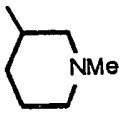
To a 2.03 M solution of boron trichloride (25 × 1.2 mmol) in toluene (14.8 ml) is dropwise added a solution of 4-anilino-1-methylpiperidine (4.79 g, 25 mmol) in toluene (40 ml) under ice cooling and stirring, and the resultant mixture is refluxed under stirring over a period of 1 hour. The toluene is evaporated under atmospheric pressure from the reaction mixture, and the residue is mixed with 2-chlorobenzonitrile (6.88 g, 25 × 2 mmol) and heated at 150°C (bath temp.) over a period of 15 hours under stirring. After cooling, the reaction mixture is mixed with 2N hydrochloric acid (15 ml) and water (30 ml) and heated at 100°C under stirring over a period of 20 minutes. After cooling, the reaction mixture is washed with ether, and the aqueous layer is neutralized with conc. aqueous ammoniac solution and shaken with methylene chloride. The methylene chloride layer is dried over anhydrous potassium carbonate and concentrated in vacuo. The residue is chromatographed on a column of alumina, which is eluted with methylene chloride. The eluate is concentrated, and the residue is crystallized from ether-petroleum ether to give 4-[2-(2-chlorobenzoyl)-anilino]-1-methylpiperidine (8.15 g) as crystals melting at 128 to 129°C. The yield is 99%.

Referential Examples 18—36

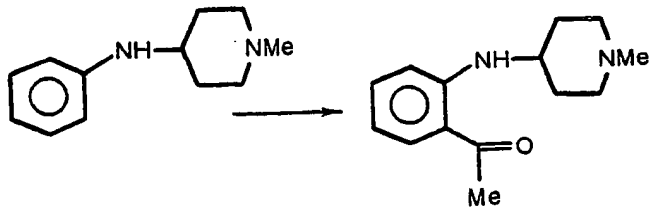
The reactions are performed as in the method of Referential Example 17, whereby the following products are obtained.



(IV)

Ref. Ex. No.	X_n	R^a	R^3	Yield (%)	mp (°C)/ IR (cm^{-1})
18	4-Cl		Ph	91	203—208 (HCl)
19	H		"	99	193—203 (2HBr)
20	"	"		95	3270 1640 (film)
21	4-Cl	"	Pb	98	3300 1620 (film)
22	"	"	2-Cl-Ph	92	101—102
23	H		2-F-Ph	97	98—100
24	"	"	4-F-Ph	96	3280 1610 (film)
25	4-Cl	"	2-F-Ph	99	3280 1610 (film)
26	3-CF_3	"	"	48	3290 1030 (film)
27	3-Cl	"	"	100	3190 1610 (film)
28	3-F	"	"	67	118—120
29	4-Br	"	"	97	3280 1620 (film)
30	4-Me	"	"	95	3280 1620 (film)
31	4-F	"	"	100	3290 1630 ($CHCl_3$)
32	3,4-Cl,Cl	"	"	86	3280 1620 (film)
33	4-Cl		2-Cl-Ph	93	3270 1620 (film)
34	"		"	95	205—209 (d)

Referential Example 35



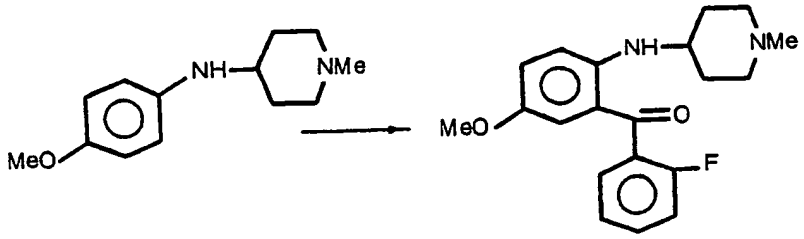
To a 2.03 M solution of boron trichloride (20 × 1.2 mmol) in dichloroethane (11.8 ml) is dropwise added a solution of 4-anilino-1-methylpiperidine (3.81 g, 20 mmol) in dichloroethane (38 ml), and acetonitrile (2.1 ml, 20 × 1.2 mmol) is added to the mixture, which is heated under reflux over a period of 20 hours. After cooling, the reaction mixture is mixed with 2N hydrochloric acid (15 ml) and water (30 ml) and stirred at 100°C over a period of 20 minutes. After cooling, the reaction mixture is mixed with conc. aqueous ammoniac solution and separated. The organic layer is washed with water, dried over anhydrous potassium carbonate and concentrated in vacuo to give 4-(2-acetylanilino)-1-methylpiperidine (4.41 g) as an oil. The yield is 95%.

IR, ν_{max}^{film}: 3260 (NH), 1630 (CO) cm^{-1}.

^1H NMR, $\delta_{ppm}^{CDCl_3}$: 1.5—3.7 (m, aliphatic H), 2.3 (s, NCH_3), 2.55 (s, COCH_3), 6.4—7.8 (m, aromatic H), 9.0 (1H, d, J=6Hz, N*H*).

Referential Example 36

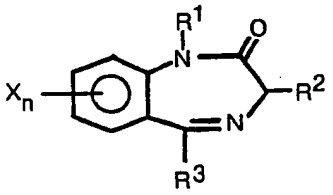
The reaction is performed as in the method of Referential Example 35, whereby the following product is obtained.



mp. 117—118°C. yield 56%.

Claims

1. A compound of the formula:



(I)

in which

R^1 is unsubstituted piperidinyl or optionally C_{1-3} alkyl-substituted pyrrolidinyl,

R^2 is hydrogen, hydroxy, or acetoxy,

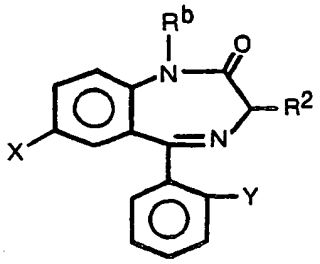
R^3 is C_{1-3} alkyl, phenyl-C_{1-3} alkyl, or phenyl optionally substituted by one or two halogens,

X is hydrogen, halogen, C_{1-3} alkyl, C_{1-3} alkoxy, nitro, trifluoromethyl, or di-C_{1-3} alkyl-amino, and

n is 1 or 2

or pharmaceutically acceptable acid addition salts thereof.

2. A compound according to claim 1, in which R^2 is hydrogen or hydroxy.
3. A compound according to claim 1, in which R^3 is phenyl optionally substituted by halogen.
4. A compound according to claim 1, in which X is halogen or nitro.
5. A compound according to claim 1, in which R^2 is hydrogen.
6. A compound according to claim 1, in which R^3 is 2-halo-phenyl.
7. A compound according to claim 1, in which X is 7-halogen.
8. A compound of the formula:



in which R^b is unsubstituted 4-piperidinyl or optionally C_{1-3} alkyl-substituted 3-pyrrolidinyl, R^2 is hydrogen or hydroxy, and X and Y each is hydrogen or halogen.

9. A compound according to claim 1, namely 7-chloro-1,3-dihydro-1-(4-piperidinyl)-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one.

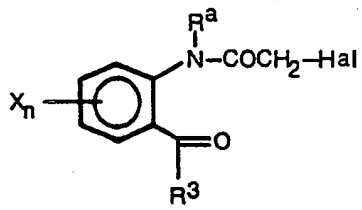
10. A compound according to claim 1, namely 7-chloro-1,3-dihydro-1-(4-piperidinyl)-5-phenyl-2H-1,4-benzodiazepin-2-one.

11. A compound according to claim 1, namely 1,3-dihydro-1-(4-piperidinyl)-5-phenyl-2H-1,4-benzodiazepin-2-one.

12. A compound according to claim 1, namely 7-chloro-1,3-dihydro-1-(4-piperidinyl)-5-(2-chlorophenyl)-2H-1,4-benzodiazepin-2-one.

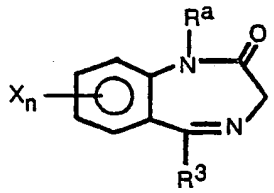
13. A pharmaceutical composition comprising a psychotropically effective amount of a compound according to claim 1 and a pharmaceutically acceptable carrier, diluent, and/or excipient.

14. A process for preparing a compound according to claim 1, which comprises reacting a compound of the formula:



(II)

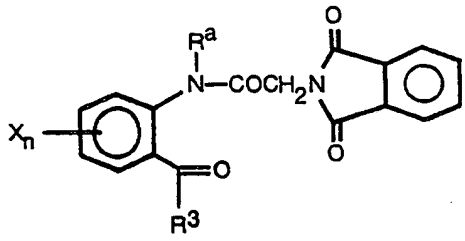
in which Hal is halogen and R^a is pyrrolidinyl or piperidinyl, each optionally substituted by C_{1-3} alkyl, phenyl-C_{1-3} alkyl, C_{1-5} alkanoyl, C_{2-5} alkoxycarbonyl or protected by amino-protecting group, and R^3, X and n each is as defined in claim 1 with ammonia or ammonium carbonate, in a solvent, at a temperature of about 15 to 150°C, so as to obtain a compound of formula



(Ia)

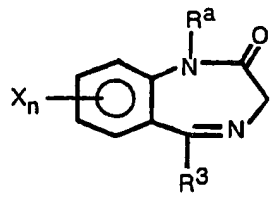
in which R^a, R^3, X and n each are the same as in the compound of formula (II) and treating, if necessary, the compound (Ia) so as to transform it into a compound of the formula (I) specified in claim 1.

15. A process for preparing a compound according to claim 1, which comprises subjecting a compound of the formula:



(III)

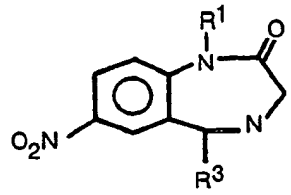
in which R^a, R^3, X and n each have the same meaning as specified in claim 14 to hydrazinolysis in a solvent at temperatures of about 30 to 160°C, so as to obtain a compound of formula (Ia)



(Ia)

in which R^a, R^3, X and n each are the same as the compound of formula (III) and treating, if necessary, the compound (Ia) so as to transform it into a compound of the formula (I) specified in claim 1.

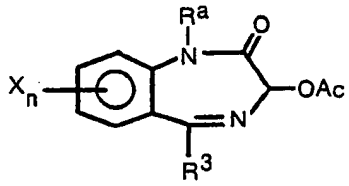
16. A process according to claim 14 or claim 15, wherein, in the compound (Ia) R^a is unsubstituted pyrrolidinyl or piperidinyl and X_n = H, and the transformation of the compound (Ia) into the compound (I) is effected by nitrating the compound (Ia) so as to obtain a compound (I) having the particular formula



(Ib)

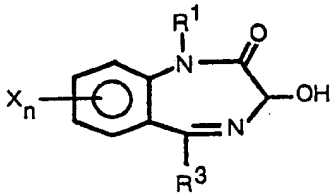
in which R^1 is unsubstituted pyrrolidinyl or piperidinyl.

17. A process according to claim 14 or claim 15, wherein, in the compound (Ia), R^a is N-protected pyrrolidinyl or piperidinyl, and the transformation of the compound (Ia) into the compound (I) is effected by oxidizing the compound (Ia), so as to form an N-oxide, and rearranging the latter by heating in the presence of acetic anhydride to afford the corresponding O-acetate (Ic)



(Ic)

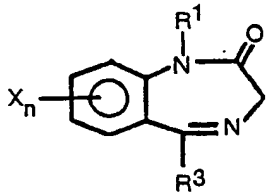
and then hydrolyzing the acetoxy group in a solvent, at a temperature of about 15 to 120°C together with the removal of the amino protecting group, so as to obtain a compound (I) having the particular formula (Id)



(Id)

in which R^1 is unsubstituted pyrrolidinyl or piperidinyl.

18. A process according to claim 14 or claim 15, wherein, in the compound (Ia), R^a is pyrrolidinyl or piperidinyl substituted by C_{1-3} alkyl or C_{2-5} alkoxycarbonyl or protected by amino-protecting group, and the transformation of the compound (Ia) into the compound (I) is effected by subjecting the compound (Ia) to removal of the N-substituent on the pyrrolidinyl or piperidinyl group in a solvent at a temperature of about 15 to 150°C, so as to obtain a compound (I) having the particular formula (Ie)

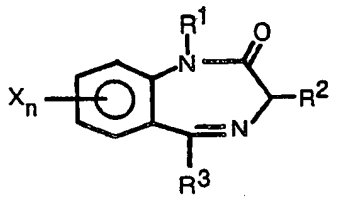


(Ie)

in which R^1 is unsubstituted pyrrolidinyl or piperidinyl.

Patentansprüche

1. Verbindung der Formel



(I)

in der
R^1 unsubstituiertes Piperidinyl oder gegebenenfalls C_{1-3} alkylsubstituiertes Pyrrolidinyl,
R^2 Wasserstoff, Hydroxy oder Acetoxy,
R^3 C_{1-3}-Alkyl, Phenyl-C_{1-3}-alkyl oder Phenyl, gegebenenfalls durch ein oder zwei Halogene substituiert,
X Wasserstoff, Halogen, C_{1-3}-Alkyl, C_{1-3}-Alkoxy, Nitro, Trifluormethyl oder Di-C_{1-3}-alkylamino und
n 1 oder 2 sind,
oder deren pharmazeutisch annehmbaren sauren Additionssalze.

2. Verbindung nach Anspruch 1, in der R^2 Wasserstoff oder Hydroxy ist.

3. Verbindung nach Anspruch 1, in der R^3 gegebenenfalls durch Halogen substituiertes Phenyl ist.

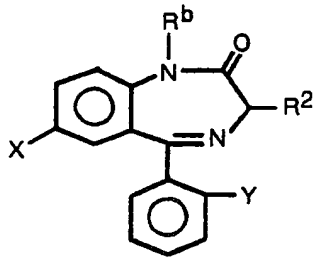
4. Verbindung nach Anspruch 1, in der X Halogen oder Nitro ist.

5. Verbindung nach Anspruch 1, in der R^2 Wasserstoff ist.

6. Verbindung nach Anspruch 1, in der R^3 2-Halophenyl ist.

7. Verbindung nach Anspruch 1, in der X 7-Halogen ist.

8. Verbindung der Formel



in der
R^b unsubstituiertes 4-Piperidinyl oder gegebenenfalls C_{1-3}-alkylsubstituiertes 3-Pyrrolidinyl,
R^2 Wasserstoff oder Hydroxy und jedes X und Y Wasserstoff oder Halogen sind.

9. Verbindung nach Anspruch 1, nämlich 7-Chlor-1,3-dihydro-1-(4-piperidinyl)-5-(2-fluorphenyl)-2H-1,4-benzodiazepin-2-on.

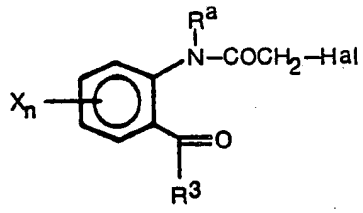
10. Verbindung nach Anspruch 1, nämlich 7-Chlor-1,3-dihydro-1-(4-piperidinyl)-5-phenyl-2H-1,4-benzodiazepin-2-on.

11. Verbindung nach Anspruch 1, nämlich 1,3-Dihydro-1-(4-piperidinyl)-5-phenyl-2H-1,4-benzodiazepin-2-on.

12. Verbindung nach Anspruch 1, nämlich 7-Chlor-1,3-dihydro-1-(4-piperidinyl)-5-(2-chlorphenyl)-2H-1,4-benzodiazepin-2-on.

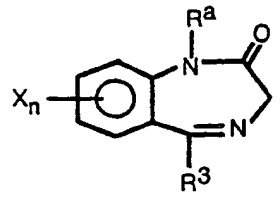
13. Pharmazeutische Zusammensetzung mit einer psychotropen wirksamen Menge einer Verbindung nach Anspruch 1 und einem pharmazeutisch annehmbaren Träger, Verdünnungsmittel und/oder Arzneimittelträger.

14. Verfahren zum Herstellen einer Verbindung nach Anspruch 1 durch Umsetzen einer Verbindung der Formel



(II)

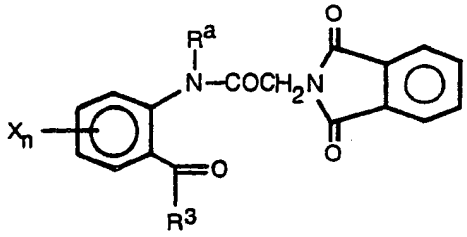
in der Hal Halogen und R^a gegebenenfalls durch C_{1-3}-Alkyl, Phenyl-C_{1-3}-alkyl, C_{1-5}-Alkanoyl, C_{2-5}-Alkoxycarbonyl substituiertes oder durch eine Aminoschutzgruppe geschütztes Pyrrolidinyl oder Piperidinyl sind, und R^3, X und n wie in Anspruch 1 definiert sind, mit Ammoniak oder Ammoniumcarbonat in einem Lösungsmittel bei einer Temperatur von etwa 15 bis 150°C, um eine Verbindung der Formel



(Ia)

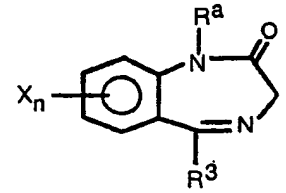
zu erhalten, in der R^a, R^3, X und n wie in der Verbindung der Formel (II) sind, und Behandeln, wenn nötig, der Verbindung (Ia), um sie in eine Verbindung der Formel (I) gemäß Anspruch überzuführen.

15. Verfahren zum Herstellen einer Verbindung nach Anspruch 1 durch Hydrazinolyse einer Verbindung der Formel



(III)

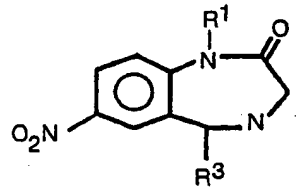
in der R^a, R^3, X und n dieselbe Bedeuten wie in Anspruch 14 haben, in einem Lösungsmittel bei einer Temperatur von etwa 30 bis 160°C, um eine Verbindung der Formel (Ia)



(Ia)

zu erhalten, in der R^a, R^3, X und n die gleiche Bedeutung wie in der Verbindung der Formel (III) haben, und Behandeln, wenn nötig, der Verbindung (Ia), um sie in eine Verbindung der Formel (I) gemäß Anspruch 1 überzuführen.

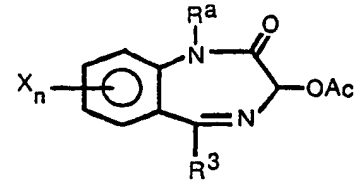
16. Verfahren nach Anspruch 14 oder 15, worin in der Verbindung (Ia) R^a unsubstituiertes Pyrrolidinyl oder Piperidinyl und X_n Wasserstoff sind, und die Überführung der Verbindung (Ia) in der Verbindung (I) durch Nitrieren der Verbindung (Ia) bewirkt wird, um eine Verbindung (I) mit der besonderen Formel



(Ib)

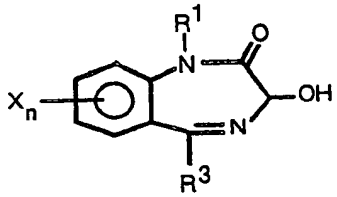
zu erhalten, in der R^1 unsubstituiertes Pyrrolidinyl oder Piperidinyl ist.

17. Verfahren nach Anspruch 14 oder 15, worin in der Verbindung (Ia) R^a N-geschütztes Pyrrolidinyl oder Piperidinyl ist, und die Überführung der Verbindung (Ia) in die Verbindung (I) durch Oxidieren der Verbindung (Ia) bewirkt wird, um ein N-Oxid zu bilden, und Umlagerung der letzteren durch Erwärmen in der Gegenwart von Essigsäureanhydrid, um das entsprechende O-Acetat (Ic)



(Ic)

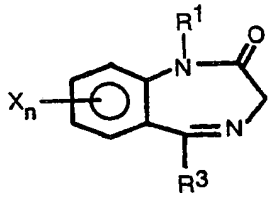
zu bilden, und anschließende Hydrolyse der Acetoxygruppe in einem Lösungsmittel bei einer Temperatur von etwa 15 bis 120°C bei gleichzeitiger Entfernung der Aminoschutzgruppe, um eine Verbindung (I) mit der besonderen Formel (Id)



(Id)

zu erhalten, in der R^1 unsubstituiertes Pyrrolidinyl oder Piperidinyl ist.

18. Verfahren nach Anspruch 14 oder 15, worin in der Verbindung (Ia) R^a durch C_{1-3}-Alkyl oder C_{2-5}-Alkoxycarbonyl substituiertes oder durch eine Aminoschutzgruppe geschütztes Pyrrolidinyl oder Piperidinyl ist, und die Überführung der Verbindung (Ia) in die Verbindung (I) durch Entfernen des N-Substituenten der Pyrrolidinyl- oder Piperidinylgruppe der Verbindung (Ia) in einem Lösungsmittel bei einer Temperatur von etwa 15 bis 150°C bewirkt wird, um eine Verbindung (I) mit der besonderen Formel (Ie)

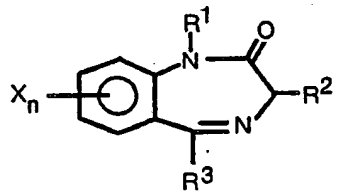


(Ie)

zu erhalten, in der R^1 unsubstituiertes Pyrrolidinyl oder Piperidinyl ist.

Revendications

1. Composé épondant à la formule:



(I)

dans laquelle

R^1 est un groupe pipéridinyle non substitué ou un groupe pyrrolidinyle éventuellement substitué par un groupe alkyle en C_1 à C_3,

R^2 est un atome d'hydrogène, un groupe hydroxy ou acétoxy,

R^3 est un groupe alkyle en C_1 à C_3, phényl(alkyle en C_1 à C_3) ou phényle substitué si on le désire par un ou deux atomes d'halogène,

X est un atome d'hydrogène, un atome d'halogène, un groupe alkyle en C_1 à C_3, alcoxy en C_1 à C_3, nitro, trifluorométhyle, ou di-alkylamino en C_1 à C_3, et

n est 1 ou 2

ou ses sels d'addition aux acides pharmaceutiquement acceptables.

2. Composé selon la revendication 1, dans lequel R^2 est un atome d'hydrogène ou un groupe hydroxy.

3. Composé selon la revendication 1, dans lequel R^3 est un groupe phényle substitué si on le désire par un atome d'halogène.

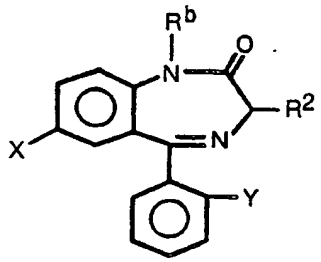
4. Composé selon la revendication 1, dans lequel X est un atome d'halogène ou un groupe nitro.

5. Composé selon la revendication 1, dans lequel R^2 est un atome d'hydrogène.

6. Composé selon la revendication 1, dans lequel R^3 est un groupe 2-halo-phényle.

7. Composé selon la revendication 1, dans lequel X est un halogène en position 7.

8. Composé répondant à la formule:



dans lequel R^b est un groupe 4-pipéridinyle non substitué ou un groupe 3-pyrrolidinyle substitué si on le désire par un groupe alkyle en C_1 à C_3,

R^2 est un atome d'hydrogène ou un groupe hydroxy, et X et Y sont chacun un atome d'hydrogène ou un atome d'halogène.

9. Composé selon la revendication 1, qui est la 7-chloro-1,3-dihydro-1-(4-pipéridinyl)-5-(2-fluorophényl)-2H-1,4-benzodiazépin-2-one.

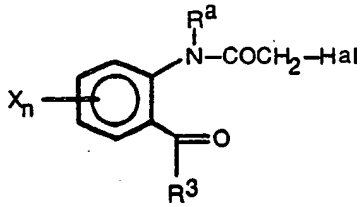
10. Composé selon la revendication 1, qui est la 7-chloro-1,3-dihydro-1-(4-pipéridinyl)-5-phényl-2H-1,4-benzodiazépin-2-one.

11. Composé selon la revendication 1, qui est la 1,3-dihydro-1-(4-pipéridinyl)-5-phényl-2H-1,4-benzodiazépin-2-one.

12. Composé selon la revendication 1, qui est la 7-chloro-1,3-dihydro-1-(4-pipéridinyl)-5-(2-chlorophényl)-2H-1,4-benzodiazépin-2-one.

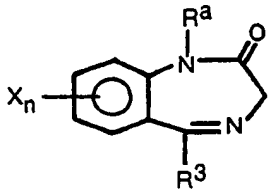
13. Composition pharmaceutique comprenant une quantité efficace comme psychotrope d'un composé selon la revendication 1 et un support, diluant et/ou excipient pharmaceutiquement acceptables.

14. Procédé pour préparer un composé selon la revendication 1, qui comprend le fait de faire réagir un composé répondant à la formule:



(II)

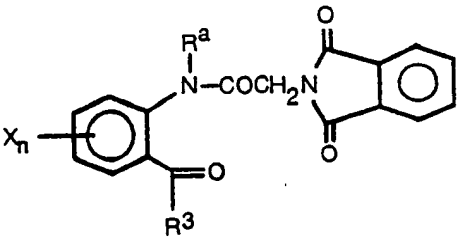
dans laquelle Hal est un atome d'halogène et R^a est un groupe pyrrolidinyle ou pipéridinyle, substitués chacun si on le désire par un groupe alkyle en C_1 à C_3, phényl(alkyle en C_1 à C_3), alcanoyle en C_1 à C_5, (alcoxy en C_2 à C_5) carbonyle ou protégé par un groupe protecteur du groupe amino, et R^3, X et n sont chacun tels que définis dans la revendication 1, avec l'ammoniac ou le carbonate d'ammonium dans un solvant, à une température d'environ 15 à 150°C, de manière à obtenir un composé répondant à la formule:



(Ia)

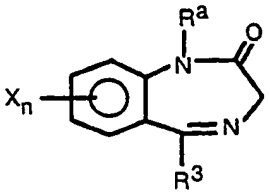
dans laquelle R^a, R^3; X et n sont chacun les mêmes que dans le composé répondant à la formule (II) et le fait de traiter, si nécessaire, le composé (Ia) de manière à le transformer en un composé répondant à la formule (I) spécifié dans la revendication 1.

15. Procédé pour préparer un composé selon la revendication 1, qui comprend le fait de soumettre un composé répondant à la formule:



(III)

dans laquelle R^a, R^3, X et n ont chacun la même signification que dans la revendication 14, à une hydrazinolyse dans un solvant à une température d'environ 30 à 160°C, de manière à obtenir un composé répondant à la formule (Ia)

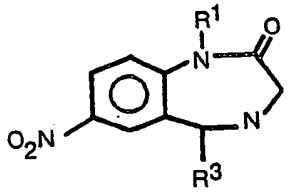


(Ia)

dans laquelle R^a, R^3, X et n sont chacun les mêmes que dans le composé répondant à la formule (III) et le fait

de traiter, si nécessaire, le composé (Ia) de manière à le transformer en un composé répondant à la formule (I) spécifiée dans la revendication 1.

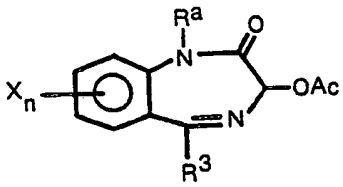
16. Procédé selon les revendications 14 ou 15, dans lequel, dans le composé (Ia), R^a est un groupe pyrrolidinyle ou pipéridinyle non substitué et X_n = H, et la transformation du composé (Ia) en le composé (I) est effectuée en nitrant le composé (Ia) de manière à obtenir un composé (I) répondant à la formule particulière:



(Ib)

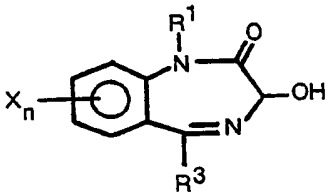
dans laquelle R^1 est un groupe pyrrolidinyle ou pipéridinyle non substitué.

17. Procédé selon les revendications 14 ou 15, dans lequel, dans le composé (Ia), R^a est un groupe pyrrolidinyle ou pipéridinyle N-protégé, et la transformation du composé (Ia) en le composé (I) est effectuée en oxydant le composé (Ia) en le composé (I) est effectuée en oxydant le composé (Ia), de manière à former un N-oxyde, et en réarrangeant ce dernier par chauffage en présence d'anhydride acétique pour obtenir le O-acétate (Ic) correspondant,



(Ic)

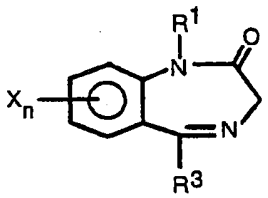
puis en hydrolysant le groupe acétoxy dans un solvant, à une température d'environ 15 à 120°C, en même temps qu'on élimine le groupe protecteur du groupe amino, de manière à obtenir un composé (I) répondant à la formule particulière (Id)



(Id)

dans laquelle R^1 est un groupe pyrrolidinyle ou pipéridinyle non substitué.

18. Procédé selon les revendications 14 ou 15, dans lequel dans le composé (Ia), R^a est un groupe pyrrolidinyle ou pipéridinyle substitué par un groupe alkyle en C_1 à C_3 ou (alcoxy en C_2 à C_5) carbonyle ou protégé par un groupe protecteur du groupe amino, et la transformation du composé (Ia) en le composé (I) est effectuée en soumettant le composé (Ia) à une élimination du substituant sur l'azote sur le groupe pyrrolidinyle ou pipéridinyle dans un solvant à une température d'environ 15 à 150°C, de manière à obtenir un composé (I) répondant à la formule particulière (Ie)



(Ie)

dans laquelle R^1 est un groupe pyrrolidinyle ou pipéridinyle non substitué.